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## ASPERGILLOSIS SECONDARY TO PULMONARY TUBERCULOSIS AND PROBLEMS IN DIAGNOSIS

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There has recently been an increase in the number of cases of various pulmonary mycoses diagnosed in Japan. The widespread use of antibiotics and steroids, an increased interest in the diseases themselves and improved methods of diagnosis have in no small measure contributed to this increase.

In this paper will be presented a review of the cases of Aspergillosis reported in Japan, results of a survey of the occurrence of Aspergillosis among patients hospitalized for pulmonary tuberculosis, methods of diagnosis including results of a skin test and reports of illustrative cases.

### Aspergillosis in Japan

Okudaira<sup>1),2)</sup> has reported on a series of mycotic diseases diagnosed at autopsy in various parts of Japan. Of 328 cases among 29,035 autopsies, Candidiasis led with 117 cases followed by Aspergillosis with 103 cases. Cryptococcosis (36 cases), Mucormycosis (17 cases) and Actinomycosis (5 cases) were next in order. There were in addition a case of Nocardiosis and one of Chromoblastomycosis and a few cases with two or more of the aforementioned fungi in combination.

In a study conducted by Tsubura<sup>3)</sup>, 247 cases of Aspergillosis were reported. A large majority of these cases, 234 or 94.7%, involved the respiratory system. Moreover, 216 or 88% of these were secondary to other systemic diseases, only 9% occurring as primary disease with 3% undetermined.

In Table I is shown a classification and the incidence of the different types of the disease and also the incidence of primary and secondary forms. As shown in Table II, the highest incidence of secondary Aspergillosis was in pulmonary tuberculosis with 118 cases (47.8%), followed by malignant tumors with 21.5%, leukaemias with 11.3%, and other generalized systemic diseases.

Table I. Classification and incidence of cases of Aspergillosis reported in Japan. The incidence of the various types as primary and secondary forms is also shown. (Modified after Tsubura; Japan. J. Med. Mycol, Vol. 5; 7, 1964)

Type		No. of Cases & % of Tot	Primary & % of type	Secondary & % of type	Undetermined
Resp. System 234 Cases, 94.2% of Total	Bronchial	19 ( 7.0%)	1	18 (94.7%)	0
	Pulmonary	87 (35.2%)	7	77 (88.5%)	3
	Bronchopulm.	4 ( 1.6%)	0	4 (100%)	0
	Fungus Ball	61 (24.7%)	13 (21.3%)	44 (72.1%)	4
	Pleural	33 (12.4%)	1	32 (97.0%)	0
	Mixed	5 ( 2.0%)	0	5 (100%)	0
	Disseminated	25 (10.1%)	1	24 (96.0%)	0
Extrapulmonary		13 ( 5.3%)	0	12 (92.3%)	1
Total & % of Total		247 (100%)	23 (9%)	216 ( 88%)	8 (3%)

Table II. Incidence of Secondary Aspergillosis in various diseases. (Modified after Tsubura, Japan. J. Med. Mycol., Vol. 5 : 7, 1964). No. of cases and percentages for other diseases have been omitted. The percentages in the lowest line refer to % of total.

Type	Total	Pulm. Tbc.	Malig. Tumor	Leukaemia
Bronchial	19	16 (84.2%)	2	
Pulmonary	87	29 (33.3%)	29 (33.3%)	14 (16.1%)
Bronchopulm.	4	0	1	
Fungus ball	61	36 (59.0%)	2	1
Pleural	33	31 (93.9%)	0	
Mixed	5	5 (100%)		
Disseminated	25	1	13 (52.0%)	12 (48.0%)
Extrapulmonary	13	—	6 (46.2%)	1
Total	247	118 (47.8%)	53 (21.5%)	28 (11.3%)

The higher incidence of Aspergillosis in pulmonary tuberculosis may partly be accounted for by the higher incidence of tuberculosis in Japan.

It is interesting to note that among 64 case of "fungus ball" or aspergilloma in Japan the highest incidence (42 cases, 65.6%) was in pulmonary tuberculosis while in a similar series reported by Schwartz *et al.*<sup>4)</sup>, the

highest incidence was with bronchiectasis (21 cases, 40%). See Table III.

Table III-a. (After Tsubura. Japan. J. Med. Mycol., 5 : 9)

Cause of Cavity	No. of Cases
Tuberculosis	42
Bronchiectasis	5
Chronic Bronchitis or Bronchial Asthma	5
Cyst	2
Pneumonia	2
Silicosis	1
Others	7
Total	64

Table III-b. (After Baum and Schwarz, Am. J. Med., 31 : 692, 1962)

Cause of Cavity	No. of Cases
Bronchiectasis	21
Lung Cyst	4
Tuberculosis	9
Histoplasmosis	5
Pneumonia of lung abscess	6
Cancer	1
Unknown	9
Total	55

Comparison of a series of 64 cases of "Fungus Ball" reported in Japan (Table III-a) and a series of 55 cases reported in the U.S.

Aspergillosis was diagnosed more often in the long standing or advanced cases of tuberculosis<sup>3)</sup>. As many as 65% of the cases of Aspergillosis secondary to pulmonary tuberculosis had cavities. The pleural and mixed types predominated in post-surgical patients presenting with bronchial fistulae or residual cavities.

## II. Survey of occurrence of Aspergillosis in patients with pulmonay tuberculosis.

We have conducted a survey of 940 patients hospitalized for pulmonary tuberculosis in various sanatoria associated with our department. A total of 28 cases of Respiratory Aspergillosis were diagnosed. See Table IV.

Table IV. Cases of Respiratory Aspergillosis diagnosed in a survey of patients hospitalized for Pulmonary Tuberculosis.

Institute or Sanatorium	Number of Patients Evaluated	Cases of Aspergillosis Diagnosed
Tuberculosis Res. Inst. Kyoto Univ.	50	1
National Utano Sanat.	30	2
National Sanat. Hira-en.	50	1
National Sanat, Hinoso	150	2
Nat. Sanat. Shigaraki-en.	100	1
Nat. Kochi Sanat.	310	17
Kyoto Haku-ai Kai Hosp.	150	1
Kyoto Kamogawa Hosp.	50	3
Total	940	28

As with many of the other pulmonary mycoses the diagnosis of Aspergillosis is not easy. In our survey, diagnosis was based on clinical history and symptoms, physical examination, X-ray findings, examination of sputum including culture, and skin tests. Details of the skin test will be described later.

### Results

- i) Of the 28 cases diagnosed, a majority occurred in the city of Kochi in Shikoku.
- ii) Apart from 5 cases of the bronchial type and 3 of the pleural type, all in postoperative patients, the majority were of bronchopulmonary type. "Fungus ball" was seen in 14 of the cases. See Table V.

Type	No. of Cases
Bronchial	5*
Pulmonary	4
Bronchopulm.	2
"Fungus Ball"	14
Pleural	3
Mixed	—
Dissem.	—
Total	28

Table V. Classification of the cases in our series.

\* Note : all 5 cases occurred postoperatively in bronchial stump.

- iii) In one case a "fungus ball" was seen on X-ray but culture and skin test were negative. The ball was removed surgically and though *Aspergillus* was identified in the specimen, attempts to culture the fungus were unsuccessful.

### III. Case Reports

Case I. The patient was a 29 year old male office worker. He was from a farming family and was used to playing with soil from childhood. He often caught colds and at the age of fifteen had "influenza" like symptoms with thick yellowish sputum which was at times rusty. There was no high fever.

At the age of 23 years, a diagnosis of pulmonary tuberculosis of the left lung was made. The sputum was positive for tubercle bacilli on both smear and culture. He was in a sanatorium for two years and was treated with Streptomycin, PAS and INH. The sputum turned negative during his hospitalization.

On being discharged from hospital he recuperated at home without being on any drug treatment.

Two years later he was hospitalized again with a diagnosis of tuberculosis of the right lung. He had loss of weight, low grade fever and a productive cough. The sputum was positive for tubercle bacilli on smear (Gaffky IV). Within two months of treatment the sputum turned negative and the patient was discharged after a year and nine months. After discharge he was employed in an office.

He continued to have a productive cough off and on for the next nine months and in April 1962 was hospitalized at the Tuberculosis Research Institute, Kyoto University. The sputum was negative for tubercle bacilli on both smear and culture. X-ray photographs showed bilateral giant cavities, Fig. 1. After bronchography was performed the patient had a sudden attack of symptoms resembling an attack of asthma. These attacks recurred often and the amount of sputum expectorated daily increased considerably, hemoptysis being noted at times. Skin tests for several allergens were negative. The attacks were brought under control with various forms of treatment including epinephrine, IPPB, steroids and antibiotics. The patient was discharged after two years. Fig. 2 is an X-ray photograph taken on discharge. The cavities had decreased in size, but the pulmonary shadows had increased in density.

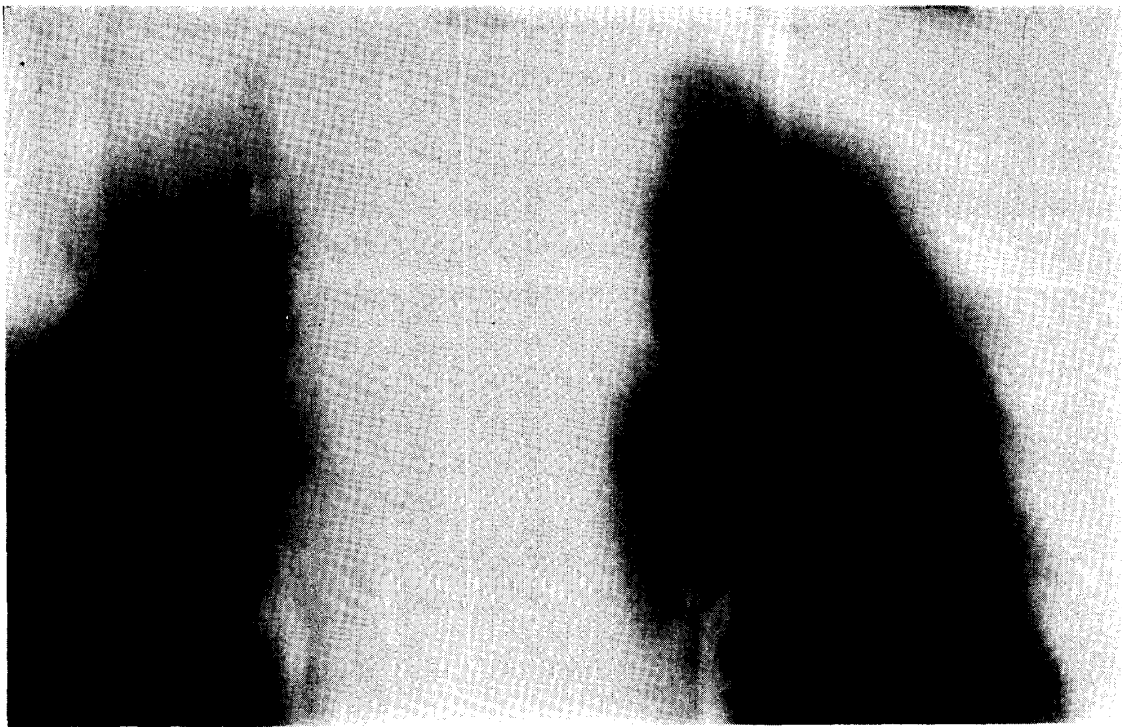


Fig. 1. Bilateral giant cavities following drug therapy for tuberculosis, Case 1.

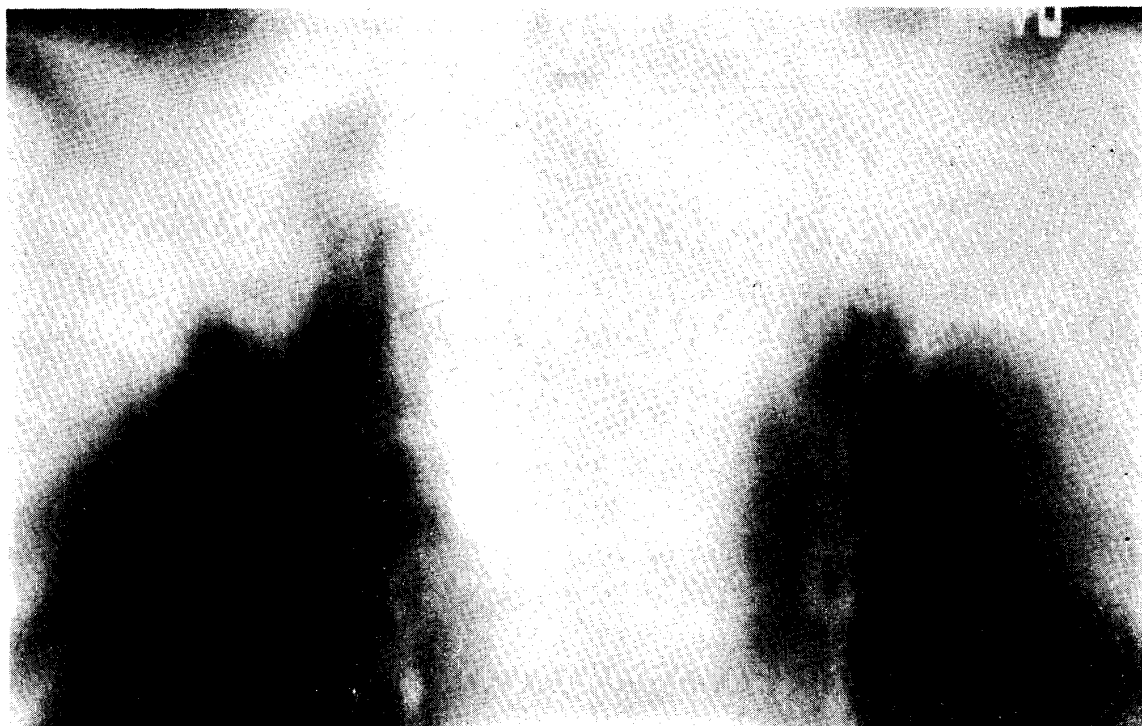


Fig. 2. Cavities decreased in size. Denser pulmonary shadows. Case 1.



Fig. 3. X-ray one year later. Fungus ball in cavity of right lung. Case 1.

During the next year the patient had a productive cough with frequent hemoptysis. An X-ray one year after the last discharge showed a "fungus ball" within the cavity in the right lung, (Fig. 3). The patient was hospitalized with a tentative diagnosis of Aspergillosis. On the second hospital day the patient had a body temperature elevation to 40 degree C, to 39 deg. on the 3rd day and it gradually came down to normal by the 6th day. Laboratory examination revealed an elevated sedimentation rate, 42 mm. in 1 hour and 68 mm. in 2 hrs., and a leucocytosis-(WBC 12,100)-with monocytosis (11%) and a slight eosinophilia (6.5%). In skin tests for Aspergillosis a positive reaction (10×10 mm. in 48 hrs.) for *Asp. fumigatus* and a weakly positive reaction (7×7 mm., 48 hrs.) for *Asp. nidulans* were obtained. On using the test for *Asp. fumigatus* and *nidulans* together a strongly positive reaction (20×25 mm. in 48 hrs.) was obtained. The sputum culture showed *Aspergillus fumigatus*, (See fig. 4 and 5). Also, two colonies were obtained from a urine specimen collected by catheterization. Owing to financial difficulties the patient was discharged without any treatment.

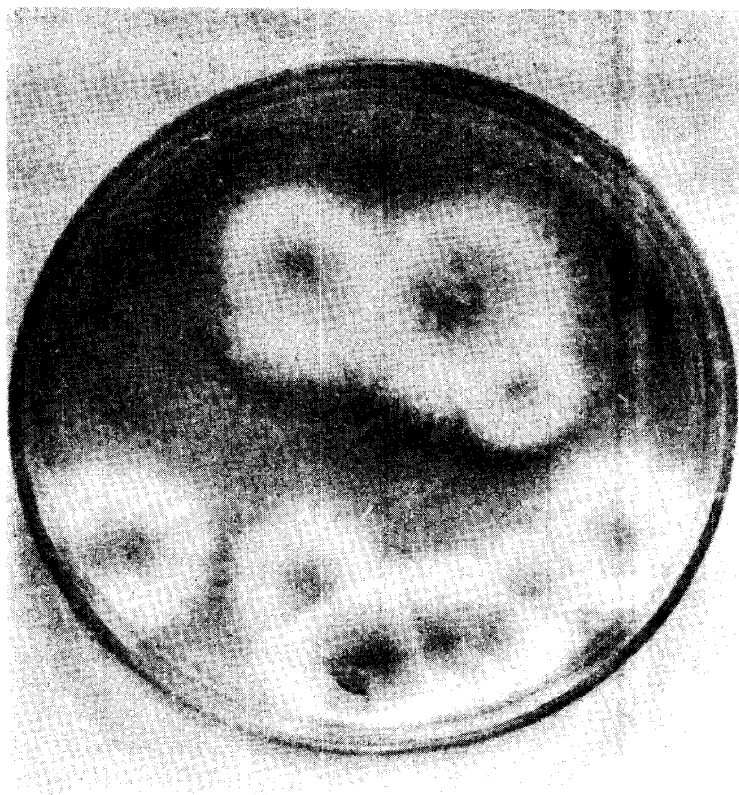


Fig. 4. Colonies of Aspergilli grown from sputum. One week at 37 C in Sabouraud's agar. Case 1.



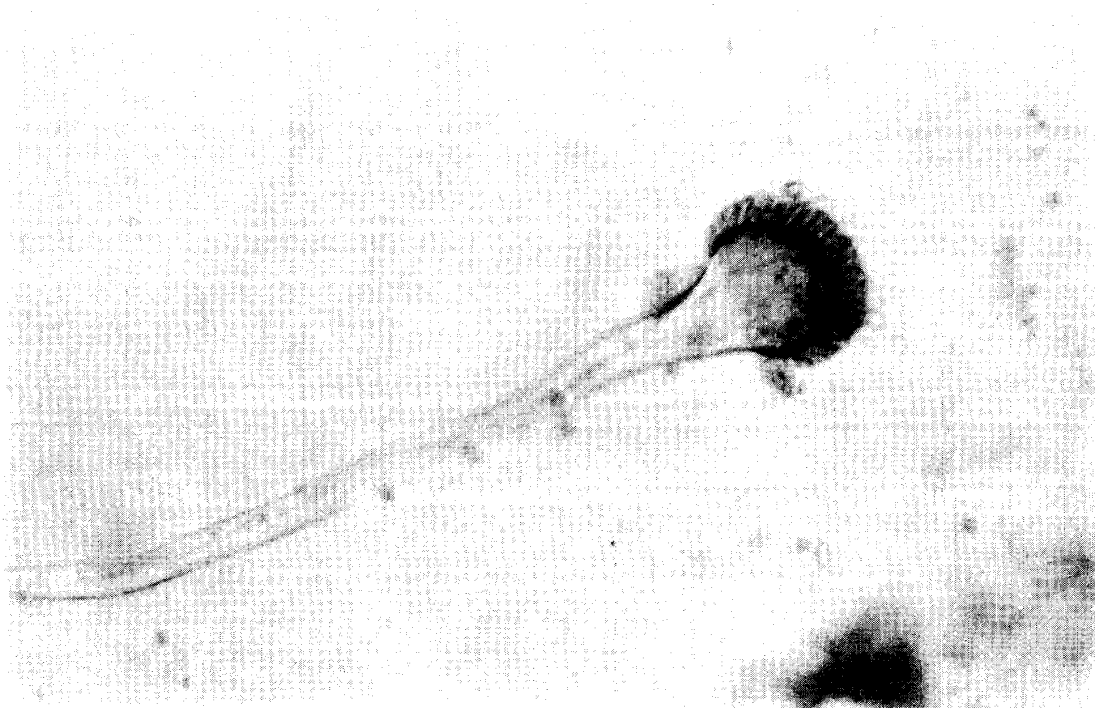


Fig. 5. Spore head ( $\times 700$ ). Identified as *Asp. fumigatus* from colony characteristics of fig. 4 and microscopy. Case 1.

Case 2. The patient was a 21 year old female. About two years prior to to the diagnosis of Aspergillosis, the patient was diagnosed as having bilateral pulmonary tuberculosis with a giant cavity in the right lung. About six months after chemotherapy the large cavity in the right lung persisted, Fig. 6.

A year and a half later the chest X-ray showed a fluid level in the cavity. Subsequently the cavity decreased in size but the shadows were denser. See Fig. 7. The patient had increased cough and sputum. The erythrocyte sedimentation rate was elevated (90 mm. in 1 hr.), sputum culture was negative for tubercle bacilli, skin test for Aspergillosis was positive and *Asp. fumigatus* was found on sputum culture. The patient was treated with potassium iodide and fungistatic drugs. Some relief was obtained.

Surgery was performed a year later. As right upper lobectomy was not feasible the R.U.L. bronchus was divided, the cavity was opened, its interior cleaned, and sutured. Aspergilli were identified in the pathological specimen. (See Fig. 8) *Asp. fumigatus* was identified on culture.

Case 3. The patient was a 55 year old male construction worker who was admitted in May 1963, with a diagnosis of pulmonary tuberculosis. For five years prior to admission he had been on chemotherapy for tuberculosis as an out-patient without any improvement in his condition. On admission he had

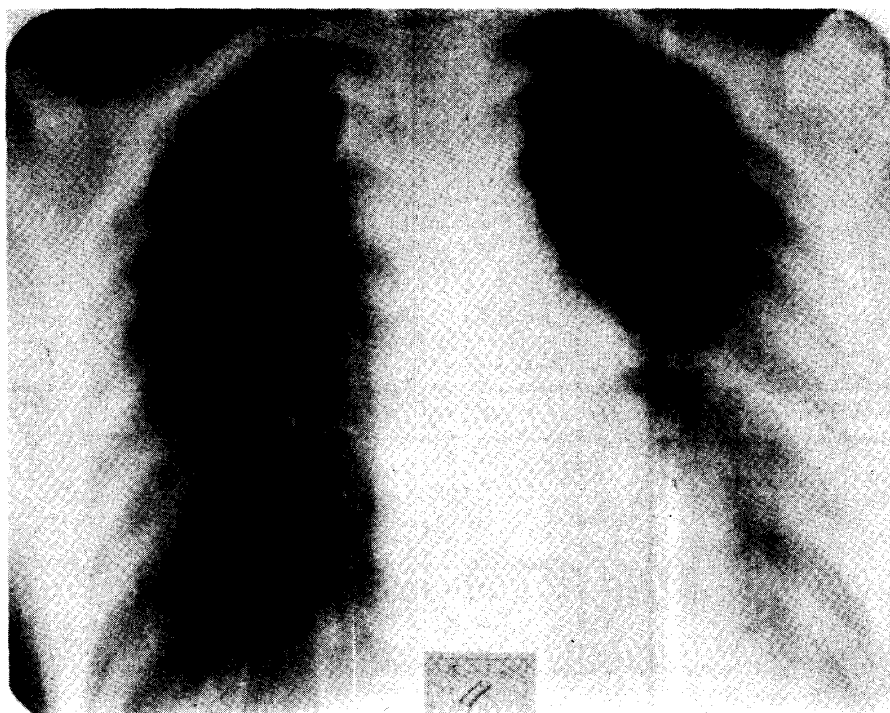


Fig. 6. Giant cavity in right upper field after 6 months of chemotherapy for tuberculosis. Case 2.

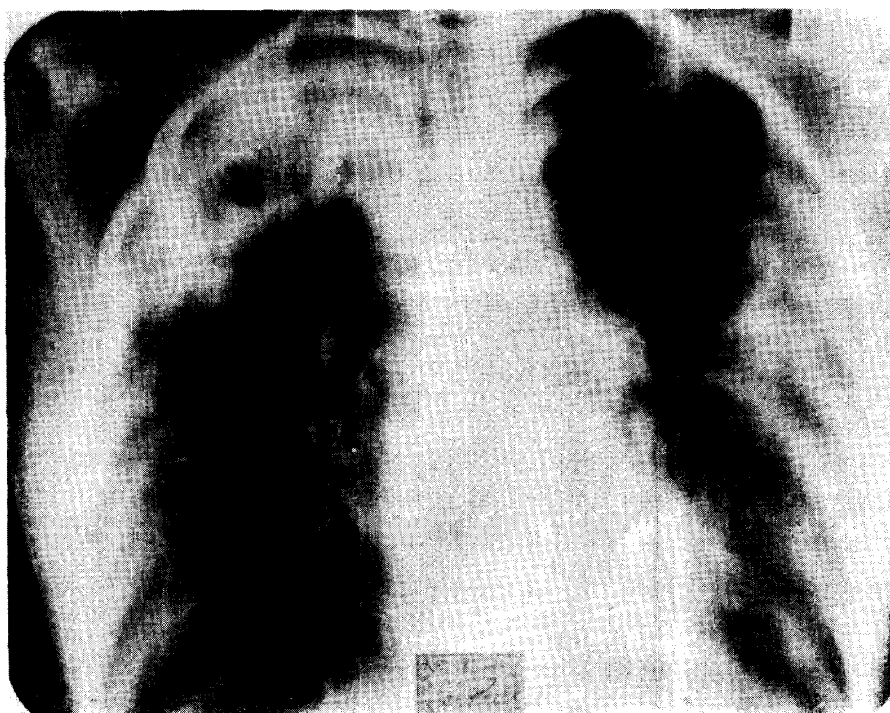


Fig. 7. Increased density particularly around the cavity. A fluid level was seen on an X-ray 1 month prior to this X-ray. Case 2.

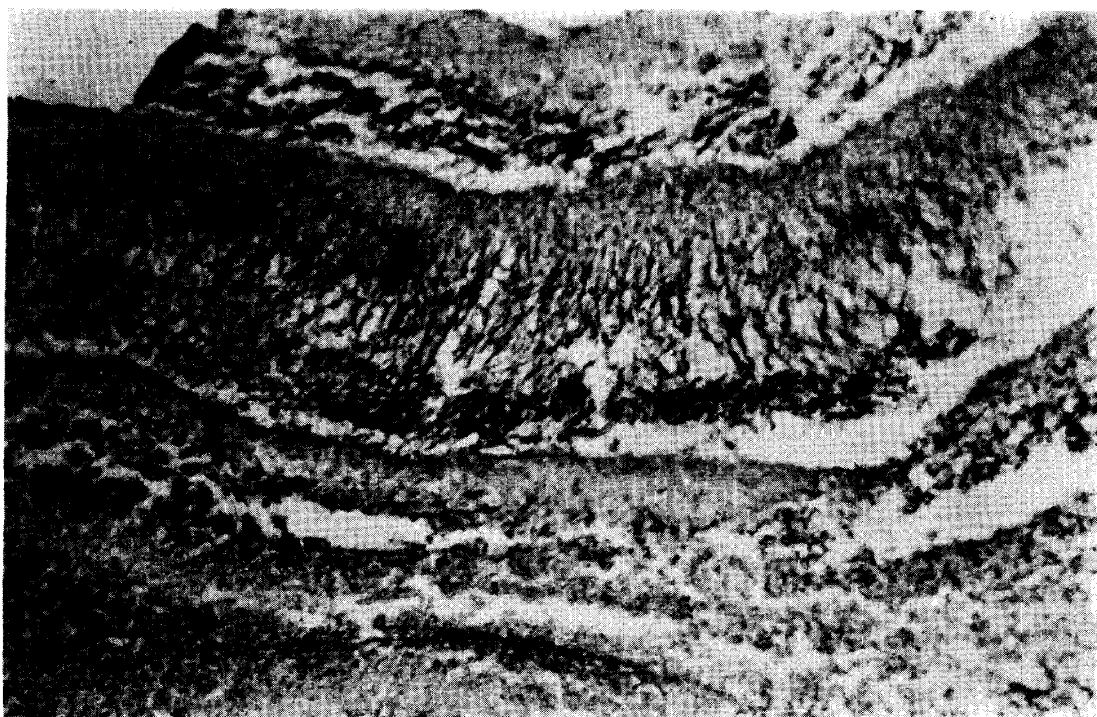


Fig. 8. Microscopic specimen of resected lung tissue. Hyphae can be seen. Case 2.

a large cavity in the left lung on X-ray and sputum smear and culture showed tubercle bacilli (Gaffky III). Fig. 9 shows the chest X-ray on admission. After three months of chemotherapy the sputum was negative for bacilli on smear and culture.

About six months later, however, his condition took a turn for the worse. Fig. 10 shows the chest X-ray taken at this time. The sedimentation rate was 130 mm. in 1 hour. Tomograms showed a "fungus ball" in the left lung (Fig. 11), the sputum was positive for *Aspergillus* on smear and culture, and the skin test was positive.

The patient's condition gradually worsened and he died in March 1963, while in hospital.

Case 4. The patient was a 24 year old fisherman in whom an abnormal shadow in the left upper lung field was noted on chest X-ray. Tomograms revealed a "fungus ball", Fig. 12. The patient had no cough, sputum or hemoptysis.

The sedimentation rate was normal and smears and cultures of sputum were negative for tubercle bacilli as well as for *Aspergillus*. The skin test for Aspergillosis was negative.

A left upper lobectomy was performed. Fig. 13 shows the resected lobe and the "fungus ball". *Aspergillus* was obtained from the "fungus ball" (Fig. 14) but could not be grown on culture.

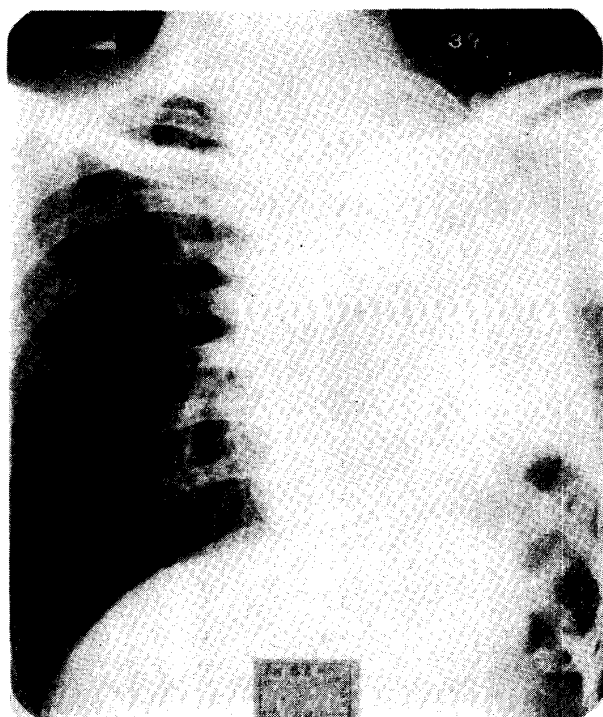


Fig. 9. X-ray on admission, Case 3. A large cavity is seen in the left upper lung field.

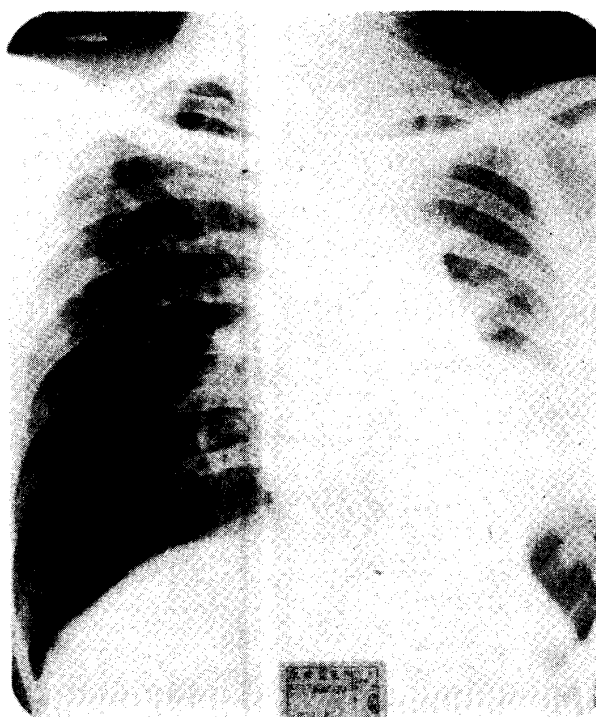


Fig. 10. Chest X-ray months after admission, Case 3. Increased opacity with decrease in size of cavity. See tomograms.

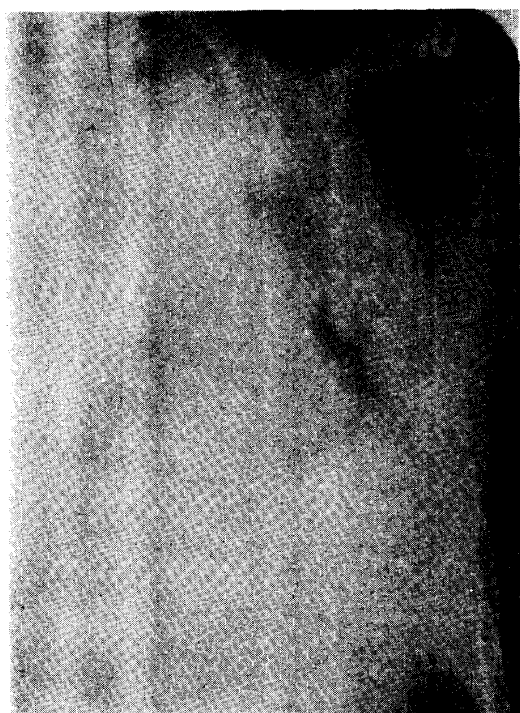


Fig. 11. Tomogram (10 cm). Several small "fungus balls" were seen.



Fig. 12. Tomogram showing fungus ball. Case 4. A left upper lobectomy was performed.

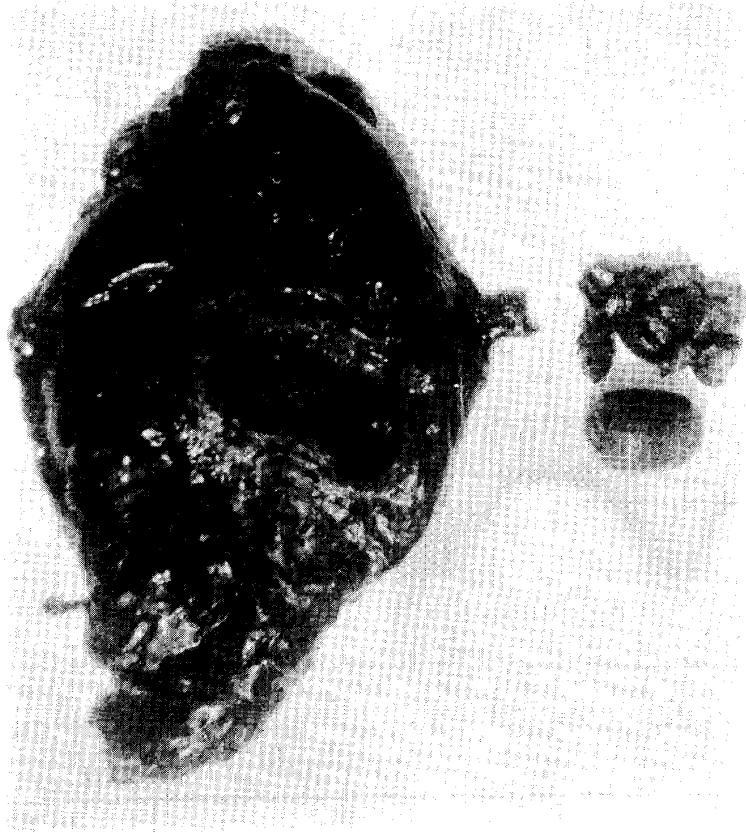


Fig. 13. Resected L.U.L. and fungus balls. Case 4.

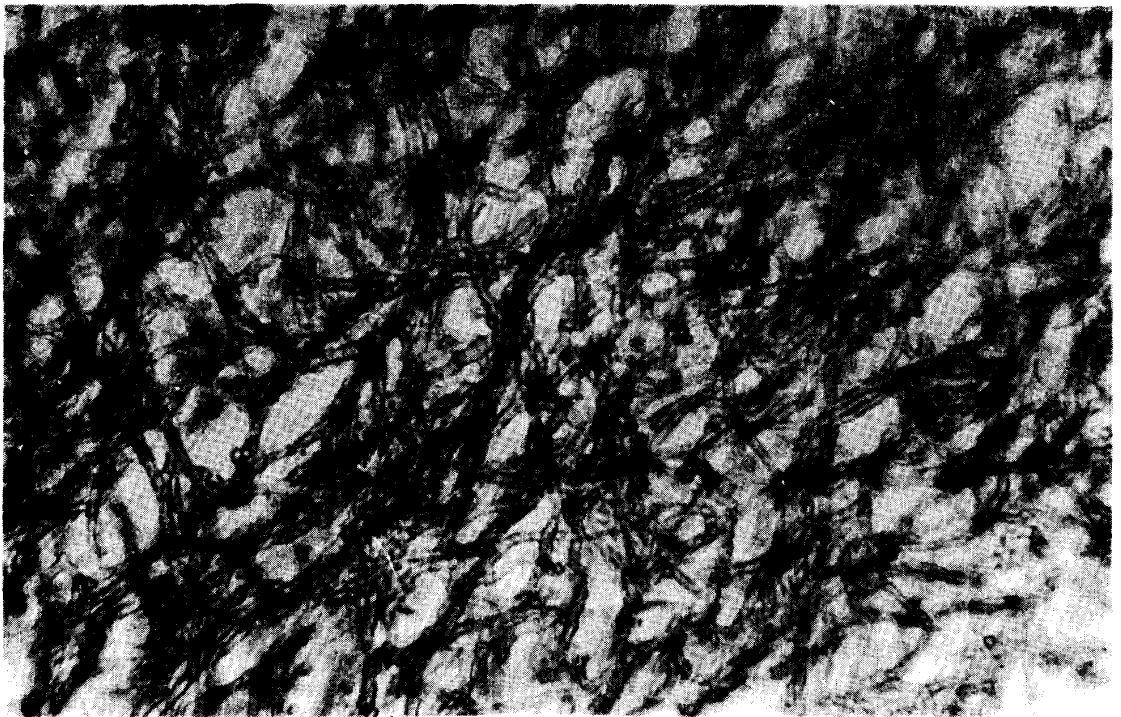


Fig. 14. Histological section of fungus ball showing numerous hyphae. There was no growth on culture. Case 4.

#### IV. Skin test for Aspergillosis

In the diagnosis of Aspergillosis we are using the filtrate from cultures of *Asp. fumigatus* and *nidulans* for an intracutaneous skin test. Favourable results have been obtained and our investigations are being continued.

##### i) Preparation of Antigen.

1. Culture in 100 cc. Sabouraud's liquid culture medium at 37 degrees C. for 3 weeks.
2. Autoclave at 120 C for 15 minutes.
3. Filtration through filter paper.
4. Filtration through Berkefeld N filter.
5. Autoclave filtrate at 120 C for 15 min.
6. Add 0.01% merthiolate for preservation.

##### ii) Preparation of Control

The same procedures as in the preparation of the antigen are repeated using Sabouraud's medium alone without inoculation.

##### iii) Method of Testing

One tenth ml. each of the antigen and control solutions diluted X 32 with physiologic saline are injected intracutaneously into the antebrachial skin of the opposite arms or into the skin of the same arm at sites 10 cm. apart. The area of erythema and induration is read at 24 and 48 hours. An area of erythema greater than 5×5 mm. with the antigen solution is considered suspicious and an area 10×10 mm. or greater is taken as positive.

We had 28 cases of Respiratory Aspergillosis. In 20 of these cases the skin test was performed and 16 reacted positively with 3 suspicious and one negative. It should be noted that there was one patient with negative culture and skin test but in whom a "fungus ball" was removed by surgery. This will be brought up in the discussion.

Altogether the skin test was performed in a total of 178 persons, 20 with

Table VI. Results of Skin Test in persons including normal subjects, patients with diagnosis of Aspergillosis confirmed and in patients with Pulmonary Tuberculosis. Note : As the study was mainly done among patients in sanatoria the number of normal subjects tested is inadequate.

Results of Skin Test	In patients with Resp. Aspergillosis	In patients with Pulm. Tuberculosis	In normal persons	Total
Number Positive	16	7	0	23
Number Suspicious	3	18	2	23
Number Negative	1	110	21	132
Total number tested	20	135	23	178



Aspergillosis, 135 with pulmonary tuberculosis and 23 normal persons. Positive results were obtained in 16 of the patients with Aspergillosis, 7 of those in sanatoria with diagnosis of pulmonary tuberculosis and in no normal persons. These results are summarized in Table VI.

## V. Discussion

The diagnosis of respiratory Aspergillosis is not easy. There are no pathognomonic symptoms and the disease may be confused with many other diseases of the lungs and bronchi.

The symptoms vary with the type and location of infection. They may consist of fever, cough, and production of bloody or mucoid sputum which may contain white or brownish flecks.

Hemoptysis may be present. The patients may sometimes have asthmatic attacks, as in Case no. 1.

The X-ray picture may simulate bronchopneumonia, or constantly changing shadows may be seen. When a fungus ball or mycetoma is observed on X-ray the diagnosis is highly suspicious. Of the series of 55 cases of fungus ball reviewed by Schwarz *et al.*<sup>4)</sup>, 48 were shown to be Aspergilloma. The disease may also be confused with pulmonary tuberculosis.

The disease has been divided into primary and secondary forms. In this discussion, comments will be restricted to the secondary form.

Decreased local and generalized resistance appear to be contributory factors in the occurrence of the disease. Debilitating diseases, prolonged use of antibiotics and chemotherapy, use of corticosteroids and "anti-tumour" drugs and irradiation all seem to be predisposing factors. For example, pulmonary tuberculosis is a chronic disease which necessitates prolonged chemotherapy; irradiation, "anti-tumour" drug and steroids are used in the treatment of malignant disease; it is in such instances that we find a higher incidence of secondary Aspergillosis. When the clinical history, symptoms and signs are suggestive of the diagnosis, confirmation may be obtained by laboratory methods including smear and culture of sputum and examination of histologic specimens.

Demonstration of hyphae in sputum, growth of the organisms on culture, morphological characteristics of the culture and microscopic examination of the cultures would all aid in the diagnosis. Aspergilli are ubiquitous and are frequent contaminants in clinical specimens. Finegold *et al.*<sup>5)</sup>, point out that in the absence of histological material the diagnosis should be made with care, although repeated isolation of Aspergilli in a suspicious case would

make the diagnosis more obvious. It has often been suggested that specimens for culture should be obtained by bronchoscopy. While this can be done in centers where bronchoscopy is available, it is not feasible in all patients and in areas where facilities are not available. Other laboratory tests are not conclusive. A leucocytosis may be present and eosinophilia may be seen in some patients. Fukushima<sup>6)</sup> reports eosinophilia in 52 of a series of 163 patients. In the same paper, he reported that leucocytosis occurred in 53 out of 204 patients.

We have developed a skin test in the hope that it may be an asset in the diagnosis. The results have been gratifying.

Experimental studies were initially performed on rabbits. In clinical studies the test was performed in varying dilutions starting with a dilution of  $\times 1000$ , followed by  $\times 100$ ,  $\times 50$ ,  $\times 25$  and  $\times 10$ . There was almost no reaction with a dilution of  $\times 1000$ ; with  $\times 100$  the reaction was very weak. The best dilution was found to be between  $\times 25$  and  $\times 50$ , and now we use a dilution of  $\times 32$ .

No untoward side effects or anaphylactic shock have been observed and we feel that the test can be applied safely.

The test was positive in 16 of 20 cases of proven Aspergillosis in our series. There was one case in which the skin test was negative, but an Aspergilloma was removed surgically.

We have also had cases in which the skin test turned negative spontaneously. The implications of these are subjects for further study.

We are of the opinion that the reaction to the skin test is of the delayed hypersensitivity type. This hypersensitivity may be transient, unlike the reaction to the tuberculin skin test. This may explain why some persons who had positive reactions initially, were later found to have negative reactions.

In Case Report No. 4 the patient had a negative skin test although an aspergilloma was present in the surgical specimen. One explanation for the negative skin test would be that the Aspergilli were saprophytic thus causing no reaction on the part of the host. It should be noted that apart from the abnormal chest X-ray findings, the patient was entirely asymptomatic.

Finegold *et al.*<sup>5)</sup> classify secondary Aspergillosis into three forms: localized, invasive and disseminated. The localized form is further divided into i) a saprophytic process consisting of a mycetoma (fungus ball) or focal growth, and ii) a chronic low grade infection, abscess or granulomatous process.

At the moment we are conducting a study among a larger group of



individuals in whom both the skin test and repeated sputum cultures are being performed. The correlation between positive skin test and positive culture will be reported in a future paper. There are at present some 13 species of *Aspergillus* known. We use the filtrate of only two species, *Asp. fumigatus* and *Asp. nidulans*, in the skin tests. Sometimes, when we had used the filtrates separately we have obtained a stronger reaction to one than to the other. Whether we have to use the filtrate of a large group of species or whether there is an antigen common to all the species are also problems that we are investigating.

### Summary

Data on cases of pulmonary aspergillosis occurring in Japan; results of a survey of pulmonary aspergillosis occurring in patients with pulmonary tuberculosis and preliminary reports on a diagnostic skin test are presented in this paper. Aspects of the skin test that demand further studies are discussed.

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